Remarks:

This is in response to the Office Action in the above-referenced application, mailed November 5, 2002. A response or other action is initially due February 5, 2003. Accordingly, this response is timely filed. Reconsideration of the application in view of the following amendments and remarks is respectfully requested.

Claims 1-3, 6-9, 35-38 and 42 were examined in the Office Action dated November 5, 2002.

Claim 2 was rejected under 35 U.S.C. §112, second paragraph, as indefinite for reciting "about."

Claims 36-37 were rejected under 35 U.S.C. §112, first paragraph, as containing new matter.

Claims 1-3, 6-9, 35-38 and 42 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

Claims 1-3, 6-9, 35-38 and 42 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not supported by written description.

Claims 1-3, 6-9, 35-38, and 39 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Gursoy *et al.* in view of Nagy *et al.*

These rejections are believed to be overcome in part by the above amendments and are otherwise traversed for the reasons discussed below.

Overview of the Above Amendments:

Claim 1 has been amended to recite that the isolated peptide is selected from the group consisting of SEQ ID Nos. 1-8. The amendment finds support in the claims as originally filed.

Claim 2 has been amended to recite that the isolated peptide sequence comprises from 4-30 amino acid residues. The amendment finds support at page 2, lines 33-35 of the application as filed.

Claim 37 has been amended to recite that the drug is coupled with an isolated peptide sequence of SEQ ID NO. 8, wherein the peptide sequence further comprises penicillamine. The amendment finds support in the sequence listing which accompanies the application, page 5 of the application and Example 2.

Claim 42 has been amended to recite that the peptide is SEQ ID NO: 8. The amendment finds support throughout the specification, such as in Example 2.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested. Claims 1-2, 6-9, 35, 37-38 and 42 are presently pending.

Addressing the Examiner's Rejections

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claim 2 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for reciting "about." The applicants have amended the claim to remove the recitation, thereby making the rejection moot.

Rejections Under 35 U.S.C. §112, First Paragraph

(a) The Examiner rejected claims 36-37 under 35 U.S.C. §112, first paragraph, for allegedly containing new matter. The applicants have amended the claims to remove the alleged new matter, thereby making the rejection moot.

(b) Claims 1-3, 6-9, 35-38 and 42 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner acknowledges that the specification is enabling for a conjugate comprising drugs recited in claim 7 coupled with a peptide of SEQ ID No: 1-8 (page 3, paragraph 11 of the Office Action), but is not enabling for any conjugate comprising any drug coupled with any isolated peptide sequence selected from the group consisting of peptide sequence derived from ICAM-1 and LFA-1.

The test for enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation." United States v Telectronics, Inc. 8 USPQ2d 1217 (Fed. Cir. 1988); In re Wands, 8 USPQ2d 1400 (Fed Cir. 1988). Thus, in order to satisfy Section 112 regarding enablement, the specification need only set forth such information as is sufficient to allow one of ordinary skill in the art to make and use the invention. How such a teaching is accomplished, either by the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367

(CCPA 1971)). The burden is on the Office to explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the Office must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Office has failed to provide adequate evidence to support the present rejection. Without such evidence, a rejection under 35 U.S.C. §112, first paragraph for lack of enablement cannot be sustained.

The Examiner acknowledges that the conjugate comprising drugs recited in claim 7 coupled with a peptide of SEQ ID No: 1-8 are enabled. Further, the specification provides detailed instructions for obtaining a drug peptide conjugate in Example 2. Thus, following the instructions provided in the specification, one of skill in the art would be able to make a drug-ICAM-1 and LFA-1 conjugate. However, in order to further prosecution, the applicants have amended the claim 1 to recite that the peptide sequence is selected from one of SEQ ID Nos. 1-8. The Examiner is respectfully requested to withdraw the rejection.

(c) The Examiner has rejected claims 1-3, 6-9, 35-38 and 42 under 35 U.S.C. §112, first paragraph, as allegedly not supported by written description. Applicants have now amended claim 1 to recite that the peptide sequence is selected from one of SEQ ID Nos.1-8. The Examiner is respectfully requested to withdraw the rejection.

Rejections of the Claims Under 35 U.S.C. §103

The Examiner has rejected claims 1-3, 6-9, 35-38, and 39 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Gursoy *et al.* in view of Nagy *et al.*

The applicants traverse the rejections and supporting remarks as the references cited by the Office do not teach or suggest the claimed invention. In order to render claims obvious, the burden is on the Office to establish a *prima facie* case of obviousness for which three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The stated combination fails to satisfy these criteria.

Gursoy *et al.*, the primary reference, does not teach peptides consisting of SEQ ID NO. 1-8, and it further does not teach that the peptides can be conjugated with drugs, such as methotrexate, lovastatin, taxol, ajmalicine, vinblastine, vincristine, cyclophosphamike, fluorouracil, idarubicin, ifosfamide, irinotecan, 6-mercaptopurine, mytomycins, mitoxantrope, paclitaxel, taxol, pentostatin, plicamycin, topotecan, fludarabine, etoposide, doxorubicin, doxotaxel, danorubicin, albuterol, or propidium, for example. The primary reference thus does not disclose all the elements of the claims.

The secondary reference Nagy *et al.* does not provide the elements missing from the teachings of Gursoy *et al.* Nagy *et al.* discloses methotrexate can be covalently conjugated to

sematostatin analog or two analogs of luteinizing hormone-releasing hormone. The coupling of the analogs with methotrexate is perfomed using an activation agent and a coupling agent. The reference does not disclose teach peptides consisting of SEQ ID NO. 1-8. Furthermore, it does not teach that the peptides can be conjugated with drugs, such as methotrexate, lovastatin, taxol, ajmalicine, vinblastine, vincristine, cyclophosphamike, fluorouracil, idarubicin, ifosfamide, irinotecan, 6-mercaptopurine, mytomycins, mitoxantrope, paclitaxel, taxol, pentostatin, plicamycin, topotecan, fludarabine, etoposide, doxorubicin, doxotaxel, danorubicin, albuterol, or propidium, for example, as claimed in dependent claim 7. Thus, the references when combined do not teach or suggest that peptides consisting of SEQ ID NO. 1-8 could be conjugated to drugs. Since, the combination of the references do not disclose all the elements of the claims, a *prima facie* case of obviousness has not been presented by the Office.

Further, the motivation to combine is said to be provided by the use of such conjugates as carrier molecules for different chemotherapeutic agents in cases in which direct action of these peptides on the membrane receptors could be established. The need to specifically target a receptor or a particular cell type are generalized scientific goals that cannot substitute for the particularity needed to establish a *prima facie* case of obviousness. The Examiner must show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet,* 47 USPQ2d at 1458, 1453 (Fed. Cir. 1998). Thus, the motivation to combine must be found within the references cited, and the required

evidence cannot be substituted with a generalized scientific goal, as the Examiner has done in the present case.

The particularity needed to establish a motivation to combine references was further discussed in *In re Lee,* 61 USPQ2d 1430 (Fed. Cir. 2002). In *In re Lee*, the Board determined that it was not necessary to present a source of a teaching, suggestion, or motivation to combine the references because the conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art. The court reversed the Board of Patent Appeals and Interferences' decision and stated: "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent ... cannot be dispensed with. The need for specificity pervades this authority." The Federal Circuit further stated that omitting the need for a specific suggestion in a particular reference to support the motivation to combine was both a legal error and arbitrary agency action (at 1434). Thus, the motivation to combine must be found in the references themselves, and the requirement is a critical safeguard against hindsight reconstruction to arrive at the applicants' invention. The references when combined do not teach or suggest peptides consisting of SEQ ID NO. 1-8, and do not teach that the peptides could be conjugated to drugs. Thus, in the present case, the Examiner has not met the required specificity to establish a motivation to combine the references.

In the absence of some teaching or suggestion in the cited references concerning the method of the present invention, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. As stated by the Court of Appeals for the Federal Circuit

In re Fine, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

The cited references do not provide a motivation to combine the references as suggested by the Examiner. Accordingly, a *prima facie* case of obviousness has not been presented by the Office. Therefore, withdrawal of the rejection under section 103(a) is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Any additional fee which is due in connection with this amendment should be applied against our Deposit Account No. 19-0522.

Respectfully submitted,

By _____

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ATTORNEYS FOR APPLICANT(S)

"Version with markings to show changes made."

In the Claims:

Please cancel claims 3 and 36 without prejudice or disclaimer.

Please amend the following claims:

1. (Amended) A conjugate comprising a drug coupled with an isolated peptide sequence selected from the group consisting of [peptide sequences derived from ICAM-1 and LFA-1] SEQ ID Nos. 1-8.

2. (Amended) The conjugate of claim 1, said isolated peptide sequence having from [about] 4-30 amino acid residues.

37. (Amended) The conjugate of claim [36] 1, wherein the drug is coupled with an isolated peptide sequence of SEQ ID NO. 8 and wherein the peptide sequence further comprises [said non-natural amino acid being] penicillamine.

42. (Amended) A conjugate comprising a first portion and a second portion, wherein said first portion [comprising] is a peptide and said second portion [comprising] is a drug, said peptide being derived from ICAM-1 or LFA-1and being characterized by binding to LFA-1 or ICAM-1 receptors on leukocytes and by being internalized by cells expressing at least one of said receptors.